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THE PROBLEM OF BLOOD SUBSTITUTES (A CRITICAL REVIEW)

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[Comment: The following review describes in considerable detail USSR work on blood expanders and compares USSR developments in this field with work done abroad. An extensive bibliography, here omitted, which consists of 84 USSR references and 68 foreign (non-USSR) references, is appended to the original article.]

Lately a new type of medicinal solution has been introduced on an extensive scale into clinical practice. Solutions of this type are usually referred to as blood-substitute solutions or blood expanders. More than 1,000 scientific papers have been published which deal with blood substitutes and their application. This indicates that the problem of blood substitutes has acquired a great importance at the present time.

In the review which follows we shall consider the basic literature dealing with the problem of blood-substitute solutions, using data of manifold investigations carried out by scientific workers at the Leningrad Institute of Blood Transfusion [LIPK]. We shall point out the progress achieved in this field both in the USSR and abroad and shall attempt to trace the development in work on this subject. Among reviews on this subject published in languages other than Russian, the best are those by Amberson, Gropper, Raisz and Amspacher, and Ravdin. The most comprehensive reviews in the Russian language have been compiled by T. F. Chursina and I. F. Leont'yev as well as by N. G. Belen'kiy. Among summaries of work on blood substitutes, those by A. A. Bagdasarov, I. P. Petrov, and P. L. Sel'tsovskiy are particularly valuable. In the latest work by Bell, detailed data are given on plasma substitutes which are used in the US Army.

Terminology

In regard to the terminology as applied to therapeutic solutions of this type, many differences of opinion exist.

They are most frequently called blood-substitute solutions (V. N. Shamov, A. N. Filatov), blood substitutes (A. A. Bagadasarov), blood-replacing solutions (P. L. Sel'tsovskiy), plasma substitutes (Ravdin, Koop), plasma-replacing or -substituting solutions (I. R. Petrov, P. S. Vasil'yev), fillers (or expanders -- Grooper), blood-substitute media (F. R. Vinograd-Finkel'). Some authors (T. F. Chursina and I. F. Leont'yev) call these solutions blood substitutes ["substitut" rather than "zamestitel'" or "zamenitel'"].

By giving these names to the solutions under consideration, the majority of investigators started from the assumption that the solutions must fulfill one task only, i. e., replace the blood which has been lost by the organism. In other words, the solutions ought to counteract predominantly the aftereffects of blood losses. Other investigators (V. N. Shamov, A. N. Filatov, A. D. Belyakov, Abert, Bowman, and Eichholtz) are of the opinion that these solutions, as far as their therapeutic action is concerned, must make blood transfusions unnecessary, these transfusions being carried out not only after blood losses but also in a number of other conditions and diseases.

In our opinion, the problem of terminology is of no basic significance. However, it is quite important that agreement should exist on the purpose for which blood-substitute solutions are used. We believe that these solutions should be used in practical medicine not only to combat the consequences of blood losses, but also to fulfill a number of other therapeutic functions (control of shock, dehydration, intoxication, and other conditions). For that reason it would be more accurate to call blood substitutes all solutions which are administered parenterally for a therapeutic purpose in large doses, i. e., doses exceeding 200 milliliters.

Requirements Which Must be Fulfilled by Blood Substitute Solutions

In many scientific investigations great attention is paid to the requirements which must be satisfied by blood substitutes (A. A. Bagdasarov and V. I. Kazanskiy, N. G. Kartashevskiy, P. L. Sel'tsovskiy, N. A. Fedorov, I. R. Petrov, Gropper, Maycock, Gill, and Hartman). It is considered that the basic requirements which must be fulfilled by blood substitutes are as follows: (1) removal of the consequences of blood losses by filling the blood circulation system with liquid, (2) control of shock by improving blood circulation in the system, (3) reduction of the dehydration of the organism and of acute thickening of the blood (4) control of intoxication, (5) elimination of hypoproteinemia and of debilitation of the organism, (6) stimulation of the resistance of the organism.

Accordingly one must consider the following factors:

1. The expander action of the solutions. This action is determined by the extent to which the reduced blood pressure has been raised, the length of time during which the raised pressure is kept on the level that has been achieved, the removal of hemodynamic disturbances, and achievement of a stable restoration of circulation in the blood vessels.

2. Antishock activity. The antishock effect is evaluated on the basis of the rapidity with which the subject is brought out of the state of shock and the stability and length of recovery from shock. The solution must be effective in eliminating the decompensation of circulation by mobilizing the blood reserves.

3. Antidehydration activity. In many pathological states the water metabolism of the organism is disturbed with the result that the blood usually thickens The hydrating activity of the solutions is determined by the speed with which the thickening of the blood is counteracted while moistening of the tongue gives a clinical indication of the hydrating effect. Among other important indexes are an increase in the turgor of the tissues and disappearance of the dryness of the skin.

4. Detoxifying effect. One speaks of a detoxifying effect in cases when the injection of blood substitute solution has the purpose of removing an intoxication brought about by endogenic poisons or toxic substances formed as a result of pathological conditions, [intestinal] obstruction, sepsis, etc.

5. Nutrient effect. In many diseases a disturbance of the protein balance takes place. On parenteral introduction of fully effective nutrient solutions, elimination of hypoproteinemia and improvement of the protein metabolism take place.

6. Stimulating action. This action is expressed in the stimulation of a number of organs and systems. When the stimulating action of the solution is good, there is improvement of the metabolism, improvement of the functioning of endocrine glands, and acceleration of regeneration processes. It is very important that blood formation be stimulated by the blood substitute solution and that rapid restoration of the normal composition of blood in anemia be assured by this means.

STAT

The better the total effects that are produced by a blood substitute solution, the higher is the evaluation which must be given to this solution. However, there are no solutions which would fulfill all the therapeutic requirements mentioned above to an equal degree. For that reason, it is necessary to have for practical clinical use solutions which are different in their activity. We are of the opinion that the most diverse blood substitutes must be available to modern clinics.

In addition to a high effectiveness a blood substitute solution must satisfy the following 24 requirements.

Characteristics of Blood Substitute Solutions

No	Property of the Blood Substitute Solution	Presence or Absence of Characteristic in Good Blood Substitute Solution
	(a) Therapeutic Properties	
1.	Blood substitute effect	Excellent
2.	Antishock effect	Excellent
3.	Antidehydration effect	Excellent
4.	Detoxifying effect	Excellent
5.	Nutrient effect	Excellent
6.	Stimulating effect	Excellent
	(b) Physical Properties	
7.	Isotonicity	Excellent
8.	Isooncotic characteristics	Excellent
	(c) Harmful Properties	
9.	Pyrogenecity	Absent
10.	Primary toxicity	Absent
11.	Subsequent toxicity	Absent
12.	Anaphylactogenic characteristics	Absent
13.	Changes produced in the coagulability of the blood and occurrence of bleeding from wounds after infusion of the solution	Absent
14.	Effects on the agglutination of erythrocytes upon mixing of the blood with the solution	Absent
15.	Prolonged retention of the solution in the organism	Absent
16.	Reaction in the form of nausea to rapid intravenous infusion of the solution	Absent

STAT

No	Property of the Blood Substitute Solution	Presence or Absence of Characteristic in Good Blood Substitute Solution
17.	Impossibility of introducing the solution subcutaneously intramuscularly, or intraossally	Absent
	(d) Technological Characteristics	
18.	Availability of the raw material	Plentiful
19.	Simplicity of production	Outstanding
20.	Uniformity of quality	Excellent
21.	Stability in storage	Excellent
22.	Suitability for drying	Excellent
23.	Stability of characteristics after repeated sterilization	Excellent
24.	Cost	Very low

The requirements have been formulated on the basis of the experience acquired by the author of this article and of statements made by a number of authors.

A blood-substitute solution must first of all have the following physical characteristics: 1. It must be isotonic with the blood or slightly hypertonic, but in no case hypotonic. 2. As far as its oncotic pressure is concerned, the solution must closely resemble blood plasma. The dimensions of the molecules of the solution must be sufficiently great. If the molecular weight of the particles contained in the solution is lower than 20,000, the solution is not retained in the circulation system, because the particles readily penetrate through the walls of the capillary vessels. Solutions of particles which have a very high molecular weight (above 200,000) are also of inferior value, because the viscosity of such solutions is too great. The best blood substitute solutions have a molecular weight of 50,000-100,000.

Blood substitute solutions must not possess the following objectionable characteristics: 1. The blood substitute solution must not be pyrogenic; its introduction into the brain of a rabbit must not raise the temperature of the rabbit's body by more than 0.6. 2. The solution must not possess a primary toxicity, i.e., on transfusion it must not produce any toxic phenomena either in normal animals or animals whose blood has been depleted. 3. After repeated transfusions of the solution, no subsequent toxic complications must occur and no pathological changes must be present in the organs of experimental animals when the latter are subjected to histological examination. 4. The blood substitute solution must not exert an anaphylactogenic effect and repeated infusions even after the period of maximum sensitization must be borne without any anaphylactic reactions; infusion of the solution to animals which have been sensitized with medical preparations (antitetanus serum, antigangrene serum, etc.) must not produce any symptoms of anaphylaxis; no phenomena of anaphylaxis must occur even after transfusion of the solution at the clinic to patients sensitized by reason of a pathological process (prolonged suppuration, tuberculosis accompanied by decomposition of the tissues, acute cancer cachexia, etc.). 5. Infusion of the solution must have no effect on changes in the blood coagulation of the recipient and must bring about bleeding from wounds. 6. On being mixed with the blood the solution must not produce agglutination or mutual cohesion of erytrocytes and make more difficult the determination of the blood group of the patients after transfusion. 7. The

STAT

blood substitute solution must be fully eliminated from the body within the first few days after infusion or utilized by the body but not retained as a harmful ballast in the tissues and organs for a prolonged period of time. 8. On intravenous administration the solution must not bring about nausea, retching or vascular reactions, which has been hitherto a common property of solutions containing amino acids.

The technology of production and the conditions and permissible length of storage must be such that extensive application of the solution is possible. In order that these conditions be satisfied, the blood-substitute solution must comply with the following requirements: 1. It must be derived from a readily available raw material. 2. The technology of its production must be as simple as possible. 3. In mass production of the solution, the certainty must exist that a solution of uniform quality is obtained and that the molecular weight of the dispersed particles is constant in the case of colloidal solutions. 4. The solution must not undergo any changes after storage in the liquid state under diverse conditions (low or high temperatures). 5. It must be possible to dry [evaporate] the solution for prolonged storage. 6. It is desirable that no changes occur if the blood substitute solution is subjected to repeated sterilization. 7. An indispensable requirement is that it should be possible to inject the solution not only intravenously, but also intramuscularly, subcutaneously, and intraossally. 8. The blood-substitute solution must be cheap and thus be suited for transfusions on a large scale. To summarize, a good blood substitute solution must satisfy all 24 requirements discussed above and listed in the table.

Classification of Solutions

The necessity of drawing up a classification of blood-substitute solutions arose during the past 10 years, because many solutions were developed during this time which have diverse properties and should be used when different therapeutic indications are present.

The majority of specialists in this field classify solutions according to their biological and physicochemical properties (A. A. Bagdasarov, I. R. Petrov, T. F. Chursina and I. F. Leont'yev, Buerkl de la Camp, Eichholtz). Others emphasize the therapeutic activity of the solutions. For that reason the name antishock solutions has originated, to give an example (N. F. Leoukhin, A. N. Filatov, E. M. Grozdov, S. A. Akopyan). In a number of classifications both principles are used. According to the classification by A. A. Bagdasarov and V. I. Kazanskiy (1944), all blood substitutes are subdivided into 5 groups: (1) blood components; (2) salt solutions; (3) colloidal solutions; (4) alcohol-glucose-salt solutions, i.e., stimulants; and (5) special anti-shock solutions.

According to the classification of the Central [Order of Lenin] Institute of Hematology and Blood Transfusion [TsOLIPK], blood substitute solutions can be subdivided into the following groups:

1. Natural blood substitute solutions: a. Preparations derived from isogenic blood. b. Heterogenous protein preparations.

2. Artificial blood substitute liquids: a. Salt solutions. b. Colloidal-salt solutions. c. Colloidal solutions.

3. Antishock liquids: a. Salt solution antishock liquids. b. Colloidal-salt solution antishock liquids.

STAT

In his latest work A. A. Bagdasarov discusses individually all colloidal plasma substitutes and divides them into three groups. He relegates to the first group blood substitutes which are prepared from isogenic blood (plasma and serum) and to the second group all the different heterogenous protein solutions. The third group comprises all synthetic preparations of the type of dextran and periston.

I. R. Petrov subdivides all plasma substitutes solutions into the following groups: (1) salt solutions; (2) salt solutions containing glucose; (3) colloidal solutions: (a) containing colloids of plant origin; (b) containing colloids of animal origin; and (c) containing blood components; (4) solutions of synthetic colloids; and (5) solutions containing combinations of the substances mentioned above.

A simplified classification has been proposed by P. L. Sel'tsovskiy. He subdivides all solutions into (1) natural blood substitutes which consist of components of human blood and (2) artificial blood substitutes, i.e., mixtures of different chemical substances or colloidal suspensions of heterogenous proteins.

In the classification drawn up by T. F. Chursina and I. F. Leont'yev, the homogenous and heterogenous solutions of blood components are included in one group, which is called the group of hematogenous blood substitutes. The second group includes all other solutions, which are called nonhematogenous blood substitutes. The second group is subdivided into (1) solutions of various proteins (e.g., gelatin, Hydrolyzatin, etc.); (2) solutions of polysacharides, and (3) polyvinyl alcohol in solutions of crystalloids. According to this classification, blood hydrolyzates are nonhematogenic blood substitutes, which is contrary to fact.

We will mention only three classifications out of the numerous systems proposed by foreign authors. Buerkl de la Camp (Germany) subdivides blood substitute solutions into three groups: (1) isotonic crystalloid (salt) solutions; (2) solutions containing colloids: (a) foreign colloids (gum arabic, polysacharides, polyvinylpyrrolidone.); (b) colloids of animal origin (gelatin, casein, treated animal serum, human serum, and human plasma); (3) solutions which have an effect on the capillaries (Subsidon, rutin).

Ravdin (England) differentiates between four groups of blood substitutes: (1) blood substitutes derived from human blood (plasma, serum hemoglobin); (2) modified proteins (gelatin, protein solutions derived from heterogenous blood); (3) high-molecular carbohydrates (acacia, dextran, etc.); and (4) plastics (methylcellulose, polyvinylpyrrolidone).

According to Bell's classification, which has been adopted by the US Army, one distinguishes between (1) blood substitutes derived from human blood; (2) plasma expanders, to which all colloidal solutions of carbohydrates and proteins belong; and (3) solutions of crystalloids.

In the majority of the classifications mentioned above, blood components are placed in a special group. This can hardly be regarded as correct. It seems to us that blood components cannot be regarded as blood substitutes, but should be considered as agents used in blood transfusions. As blood substitutes one may regard only solutions which contain plasma, serum, erythrocytes, or the hemoglobin of human blood in its natural or modified state added to a salt solution forming the basis of the blood substitute.

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The purpose of the addition made to the salt solution is to endow the solution of the crystalloid with colloidal properties.

We regard the following classification of blood substitute solutions as the most appropriate. According to this classification, all solutions are subdivided into three groups: (1) salt or crystalloid solutions; (2) colloidal solutions; and (3) solutions representing combinations of the above.

Classification of blood substitute solutions

1. Salt solutions

   a. Ordinary salt solutions

   b. Antishock salt solutions

   c. Therapeutically active solutions of crystalloids

2. Colloidal solutions

a. Blood substitute solutions containing components of human blood: Petrov's liquid, Serotransfusin (TsOLIPK), salt solutions containing dry plasma (LIPK), modified globin (USA), hemoglobin solution (German), Aminokrovin (LIPK).

b. Carbohydrate colloidal blood substitute solutions: (1) solutions of the dextran group: Macrodex, Introdex, Expandex, USA dextran, Oncotin, Polyglyukin (TsOLIPK), Sinkol (LIPK); (2) AP solution (LIPK; Naval Medical Academy), pectin solutions, citrus pectins, Lifshits' Stimulen solution.

c. Blood substitutes of the synthetic chemicals group (synthetic polymers): (1) solutions of methyl cellulose; (2) solutions of polyvinyl alcohol; solutions of polyvinylpyrrolidone: periston (German), Plasmosan (British), Polyvidon (USA), SK (LIPK), polyvinylpyrrolidone solution (TsOLIPK).

d. Blood substitutes which have a pharmacadynamic effect (i.e., those which exert an action on the capillary blood vessels): Subsidon (German), Adrenoxyl (Swiss).

e. Blood substitute solutions derived from proteins: (1) modified heteroproteins: Naprin (Leont'yev), colloidal infusin (TsOLIPK), Belen'kiy's therapeutic serum, heterogenous plasma (PH-British), plasma of animals which has been made nonspecific (Spanish); denatured plasma (Czechoslovak), Adequan (German), BK-8 (Kiev Institute of Blood Transfusion), nonanaphylactogenic serum S-24 (Fedorov), TsOLIPK protein solutions (Vasil'yev), KS-120 (LIPK), Parenterin (Belen'kiy); (2) hydrolizates: Amigen (USA casein hydrolizate), L-103 (LIPK), Aminol (LIPK), Aminopeptide (Military Medical Academy), casein hydrolyzate (TsOLIPK), Aminorastin (LIPK); (3) blood substitute solutions derived from gelatin: liquid gelatin, 6% solution, Plasmogel (USA), Oxypolygelatin (USA), MGG (USA), fish gelatin; (4) blood substitute solutions derived from plant proteins (e.g. Biorastin LIPK).

3. Solutions containing several ingredients. Antishock colloidal solutions (TsOLIPK, Grozdov); Akopyan antishock liquid; colloidal solutions to which amino acids have been added (USA): Aminoprotein (L-103 plus human plasma); UBP (LIPK); Colloidal Protein solution (L-103 + Sinkol); a periston solution with erytrocytic mass (German); Belyakov and Petrov's antishock solution; antishock solutions combined with blood (LIPK No 28).

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STAT

All salt solutions are divided into three subgroups: (1) ordinary salt solutions or salt solutions containing glucose; (2) antishock solutions containing anesthetics which exert an action on the nervous system; and (3) complex salt solutions, i.e., therapeutic solutions for the treatment of sepsis or other pathological conditions.

Colloidal solutions are subdivided into five subgroups: (1) blood substitute solutions which contain components of human blood; (2) carbohydrate colloidal blood substitute solutions; (3) blood substitute solutions which contain synthetic polymers; (4) blood substitute solutions which exert an action on the capillary vessels (pharmocodynamically active blood substitute solutions); and (5) blood substitute solutions derived from proteins.

Solutions containing several ingredients are obtained by combining solutions which have different properties and adding to them certain drugs. To this group belong antishock solutions to which blood has been added, the antishock colloidal solutions developed by TsOLIPK, hydrolyzates to which human plasma has been added, and the UBP solution developed by LIPK, which is a carbohydrate-protein plasma expander consisting of Sinkol to which components of human blood have been added.

In our opinion, one must produce on a mass scale salt and colloidal solutions for clinical use while solutions containing several ingredients are best prepared immediately before use by combining standard solutions and adding the drugs to them. We will now discuss each group in detail.

5. 1. Salt or Crystalloid Blood Substitute Solutions

As late as 10-15 years ago ordinary salt solutions and glucose-salt solutions (first subgroup) were the most widely used blood substitutes under clinical conditions. At present, these solutions are losing their importance to an increasing extent. As can be seen from the classifications that have been drawn up, some authors do not regard them as blood substitutes at all (T. F. Chursina and I. F. Leont'yev).

This attitude towards crystalloid solutions has developed because of their insufficient effectiveness in the treatment of conditions following blood losses and of shock. Nevertheless, as has already been stated above, the function to be fulfilled by the solution is not merely one of raising the blood pressure and keeping it at the necessary level after it has dropped subsequently to a blood loss or shock. It is true that the salt solutions do not fulfill this function in a satisfactory manner. However, one must keep in mind that when salt solutions or glucose-salt solutions are administered slowly by the drip method, they may support all vital functions even in a body which has been subjected to a severe blood loss (particularly if balanced salt solutions are used). A. A. Babskiy reported on good results achieved by the therapy of acute blood losses with a solution (AM 4) prepared from sea water.

One must agree with I. R. Petrov that salt solutions containing a hypertonic concentration of sodium chloride are most effective for the treatment of the consequences of blood losses and of shock. The reason for this is that solutions of this type have a great capacity of bringing about reflex spasms and of mobilizing blood reserves, thus stimulating the vascular chemoreceptors. By reason of their high osmotic pressure in comparison with isotonic solutions, hypertonic solutions bring about penetration of tissue liquids into the vascular system, so that more prolonged action of the solution is assured. Among solutions of this type, the No 3 solution of the Leningrad Institute of Blood Transfusion has been tested on the most extensive scale in World War II.

STAT

A great number of salt blood substitutes has been proposed. The most important of them have been mentioned in the classification scheme outlined above. In the opinion of N. N. Yelanskiy, the effectiveness of all salt solutions is approximately the same.

A great number of antishock salt solutions (second subgroup) has also been proposed (S. A. Akopyan, A. F. Lepukaln, M. A. Bubnov, D. M. Grozdov, P. L. Sel'tsovskiy, and N. A. Fedorov). Some of them were extensively used during World War II. This applies to Akopyan's liquid, P. L. Sel'tsovskiy's liquid, the alcohol-bromoglucose liquid of I. R. Petrov, V. I. Popov's liquid, A. N. Filatov's solutions No 28 and No 43, etc. All of these solutions differ from ordinary salt solutions in that they contain anesthetics and other drugs which bring about a protective inhibition of the central nervous system. In the majority of the solutions which have been mentioned, alcohol is used for this purpose.

A third subgroup of crystalloid solutions is composed of therapeutic solutions which contain drugs that are supposed to bring about a therapeutic effect in various diseases. A. D. Belayakov of the Leningrad Institute of Blood Transfusion proposed solution No 22, which contains salts, antiseptics, and antibiotics. This solution proved very effective in the therapy of suppurative infections and septic conditions.

Although salt solutions, glucose-salt solutions, antishock crystalloid solutions, and therapeutic salt solutions are not as effective in alleviating the effects of acute blood losses and shock as colloidal solutions, their use in practical clinical work should still be continued on an extensive scale (A. N. Filatov, P. A. Khanin, etc.) This recommendation should be made, because solutions of this type are of great use in counteracting dehydration, intoxication, sepsis, and shock and consequences of blood losses of a medium degree of severity. They therefore make it possible to dispense with the administration of more complex blood substitutes and blood transfusions. The advantage of these solutions consists in the fact that they can be prepared at any medical institution from readily available drugs.

2. Colloidal Blood Subutitutes

Solutions which contain molecules of a relatively larger size and approach blood as far as their colloidal characteristics and viscosity are concerned are called colloidal blood substitute solutions. While crystalloid solutions are retained in the blood circulation for no longer than 2-3 hours, colloidal solutions stay in the blood vessels for a longer time, i.e., in excess of 4 hours and in the case of some solutions even for several days.

The first subgroup of colloidal solutions consists of those which contain components of human blood. This subgroup comprises only solutions which consist essentially of ordinary salt solutions to which small quantities of plasma, serum, or human blood have been added. In these solutions, the components of human blood serve mainly the purpose of endowing the solution with colloidal properties. The effectiveness of such solutions is much superior to that of ordinary salt solutions. Among solutions of this type one must first of all mention I. R. Petrov's liquid, a salt solution prepared from salt tablets which is combined with 10% of preserved blood. Another important preparation of this type is the TsOLIPK Serotransfusin prepared according to a prescription by N. A. Fedorov and P. S. Vasil'yev. This solution consists of salt Infusin to which 20% of human serum have been added. As is well known, Petrov's liquid was extensively used during World War II.

STAT

Instead of liquid plasma, dry plasma can be added to the solution. This is of obvious advantage, because the solution can be prepared immediately before use. Since one may store for a long period the salt solution and dry plasma separately, such solutions present great advantages as compared with Serotransfusin and similar blood substitutes. Experimental work done by I. R. Petrov and N. V. Nekrasova has demonstrated the high effectiveness of such solutions in the therapy of the consequences of blood losses. Clinical observations by A. N. Filatov and A. M. Romanova have demonstrated the high effectiveness of solutions of dry plasma when administered for the prophylaxis and therapy of shock. Solutions to which hemoglobin has been added are described in scientific publications (Amberson, Thrower, Campbell, Koop), but for all practical purposes have not been used hitherto. The shortcoming of these solutions is that hemoglobin during storage is changed into the inactive methemoglobin, which is harmful to the organism. Work by I. G. Andrianova has demonstrated that this shortcoming can be eliminated: she obtained stable preparations of hemoglobin. One may, under the circumstances, regard as useful further work on hemoglobin solutions.

Solutions prepared from treated human blood are being introduced more widely into practical use. Among them are preparations of modified globulin and albumin which are used abroad (Strumia, Chorhock, Blake, Harr). When human blood that can be used as such is utilized for the preparation of such solutions, this procedure is difficult to justify. It is a different matter if the solution is prepared from residues of blood that have not been used or blood which has been salvaged. One of the solutions of this type is Aminokrovin (Z. A. Chaplygina) which has been proposed recently by the Leningrad Institute of Blood Transfusion. This solution is obtained by the acid hydrolysis of coagulated blood that remains after the preparation of antimeasles sera, of erytrocytic mass which remains after the decantation of plasma from the blood of corpses, and other unused human blood. This solution completely satisfies all clinical requirements and is suitable on the basis of all 24 characteristics which determine the quality of blood substitute solutions.

A second subgroup of colloidal blood substitutes consists of colloidal solutions of carbohydrates. Solutions of this type are referred to abroad as colloidal blood expanders.

They are used extensively in all countries and deserve a considerable amount of attention.

The first solutions of this subgroup were the acacia gum solutions proposed by Bayliss as early as 40 years ago. A considerable number of publications is devoted to solutions of this type. However, they have not been introduced into use on a large scale because of a number of drawbacks comprising insufficient effectiveness, frequent reactions and complications upon administration to the patient, difficulties in purifying them, etc., (Amberson, Holl). In the USSR literature, there are only individual communications on the subject of these solutions (N. P. Perumova). This is understandable, because the raw material for the production of this type of solution is not being produced in the USSR.

Recently, Z. M. Umanskiy, M. I. Ol'shanskiy, and M. L. Frimerman proposed that colloidal blood substitutes be prepared from apricot gum (gum armenial). A 0.5% solution of this gum combined with salts, which has been named Guasol by the authors mentioned above, proved to be an effective blood substitute in experimental work on dogs. A final judgment in regard to this solution is premature, because only a small number of experimental observations has been made.

STAT

Solutions of substances of the dextran type undoubtedly occupy a leading place at present among colloidal blood substitute solutions.

Dextran is a water-soluble, high-molecular polysachharide, the synthesis of which is effected by bacteria. When grown on media that contain sugar, bacteria of the Leuconostoc type form a slime which consists of a polymer of glucose. This is dextran. Natural dextran has a very high molecular weight amounting to several million and is not suitable for infusion. Gounwal and Ingelman were the first who became interested in using dextran as a blood substitute. By subjecting the dextran to acid hydrolysis followed by purification and fractionation, one may obtain from it an excellent blood substitute which has an ideal molecular weight within the range of 50,000-100,000.

Blood substitute dextran solutions have been prepared in many countries. They were originally produced in Sweden in 1943. The experience of Swedish physicians now comprises 40,000 cases in which dextran solutions have been administered (Thorsen). A number of different names is used by different companies for dextran solutions. They are being distributed under the names Macrodex (Sweden), Introdex (England), dextran, Macrose, Plevolex, Expandex (US), etc., (Klausendorf, Gelin). The extensive literature which exists on the subject is filled with enthusiastic evaluations of the results obtained with the use of dextran solutions. The high effectiveness of solutions of dextran upon administration subsequently to blood losses, extensive burns, and intoxication has been proven (Bowman, Dieckhoff and Bloom, Gelin, Hammerstein, Heller, Ebert, Johnston, Turner, Butler, Rosenquist, Thorsen, Tarrow, et al.)

One of the drawbacks of solutions of this type is the lengthening of the time of blood coagulation, so that increased bleeding from wounds may be produced. A heightened agglutinability of erythrocytes after infusion of dextran solutions has also been noted, an effect which is of no great importance, except that it must be taken into consideration in determining the blood group of patients who have just received an infusion of a solution of this type. There are also indications that upon repeated introduction of large doses of solutions of this type, changes in the parenchymatous organ are possible and dextran may be deposited in them (Hartman, Millican, et al). Taking all this into consideration, many authors suggest that no more than 600 milliliters of the solution be administered. In cases where an acute blood loss has taken place, it is recommended under all circumstances to supplement the infusion of the dextran solution with a blood transfusion (Bloom, Fleming and Caraill, Horvath and Hamilton, Carbone, Turth, Scott and Crosby, Nelson and Lusky, and others.)

In the USSR two solutions of the dextran type have been produced: one at TsOLIPK under the name of Polyglyukin and one at LIPK under the name of Sinkol.

In order to prepare these solutions, Soviet investigators (A. P. Vishnayakov and R. M. Shereshevskaya, T. A. Krutova, and K. M. Dvolaytskaya - Barysheva and G. S. Sel'tsovskaya) had to accomplish extensive work on the biological synthesis of dextran. Highly productive bacteria of the Leuconostoc group were isolated and their properties subjected to study.

The Poliglyukin solution, a dextran preparation developed at TsOLIPK (G. Ya Rozenberg, G. V. Polushina, R. A. Rutberg, V. A. Agranenko, and R. I. Murayan), was investigated in animal experiments and found to exhibit a high hemodynamic activity. Clinical observations established that Polyglyukin prepared from soluble dextran does not produce any reactions in patients even when administered in doses up to one liter. At present, one of the Moscow chemicopharmaceutical plants have been entrusted with the production of this blood substitute. It is to be expected that Polyglyukin will soon be supplied to medical institutions.

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The solution developed by the Leningrad Institute of Blood Transfusion, i.e., Sinkol (A. P. Vishnyakov, R. M. Shereshevskaya, T. A. Krotova, I. R. Petrov, and V. A. Bondina) has been subjected to a thorough experimental investigation (I. R. Petrov, V. A. Bondina and V. K. Kaulagin). It has been also subjected to tests in practical clinical work (B. L. Chernomordik, A. I. Goshkina). It was established that sinkol is very effective in that it restores victims who suffer from consequences of shock and heavy blood losses. It also controls intoxication and eliminates dehydration of the organism. If the solution is administered subsequently to a blood loss, one must be guided by the quantity of lost blood in establishing the condition of the patient and not by the level of blood pressure, because after infusion of Sinkol the blood pressure always goes up notwithstanding the fact that a collapse may be near by reason of the blood loss. (F. G. Uglov and Ye. I. Narbut). It is recommended that single doses of 500-800 milliliters of Sinkol be administered. If the blood loss has been acute, one must supplement the administration of Sinkol with a blood transfusion. At present the production of Sinkol on a large scale is being organized at the Leningrad Chemicopharmaceutical plant, so that this preparation will soon be available for extensive clinical tests.

Another colloidal blood substitute derived from carbohydrates is the AP solution which has been subjected to experimental investigation at the Blood Substitute Laboratory of the Leningrad Institute of Blood Transfusion (L. G. Bogomolova, I. R. Petrov, Z. A. Chapygina). The AP solution is a plasma expander which does not produce any reactions. It is obtained from very cheap carbohydrate raw material (potato starch and corn starch). Just like dextran, the substance contained in this solution is a colloidal polysaccharide. The favorable characteristics of the AP solution, which brought about with certainty the recovery of animals even after acute blood losses, makes it possible to give a very high evaluation to this blood substitute. At present, clinical tests of the AP solution have been started. The results of these tests will indicate the place which AP occupies among blood substitutes.

The pectin solutions which have been proposed in the United States as early as 1941 are another type of colloidal polysachharide solutions with a high molecular weight (40,000-60,000). The pectin is produced from fruit, principally citrus fruit. Pectin solutions also proved very effective in the therapy of shock and the consequences of blood losses (Hartman, Jacobson, Smyth, Scheling, and Harkins). The problem in regard to the retention of pectins in the organism has not yet been solved. One of the drawbacks of pectin solutions is their inadequate physical stability in heat sterilization.

It is probable that the preparation which has been named Stimulen and proposed by Lifshits is a blood substitute solution of this type (M. N. Lifshits and Ye. G. Tsurinova).

It is regrettable that little work is being done in the USSR on pectin solutions as yet. Only quite recently research on this subject has been initiated at the Leningrad Institute of Blood Transfusion.

The subgroup of blood substitutes consisting of synthetic polymers can be subdivided as follows: (1) methylcellulose solutions; (2) solutions of polyvinyl alcohol; and (3) polyvinylpyrollidone solutions.

Methylcellulose has a molecular weight in excess of 50,000. Methylcellulose solutions have been subjected to experimental investigation and clinical tests (Steuper). The data which have been obtained are contradictory. Because of the simplicity of preparation, stability in sterilization, absence of antigenic properties, and a high molecular weight resulting in good colloidal properties, these solutions have been found of advantage. On the other hand, the infusion of methylcellulose solutions was found to prolong the period of blood coagulation and expedite the sedimentation of erythrocytes. These are effects which are observed after the

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introduction of many foreign colloids. Doubts have also arisen on the score
of the possible toxicity of methylcellulose and the chance that its retention
in the organism may represent a danger. Further experimental and clinical
investigations are needed in order to arrive at a final decision in regard to
the use of methylcellulose solutions (T. F. Chursina and I. F. Leont'yev.)

Solutions of polyvinyl alcohol have been used with great success in
the therapy of shock and the alleviation of consequences of blood losses both
under experimental conditions and at the clinic. Just like other colloidal
solutions of high polymers, polyvinyl alcohol has the advantage of being re-
tained for a long time in the vascular system of the recipient. Experiments
in which the vascular system of animals was overloaded with polyvinyl alcohol
solutions showed that there is a possibility of the formation of harmful de-
posits of this foreign colloid in the organism. For that reason, one should
administer polyvinyl alcohol solutions in small quantities only (up to one
liter) and restrict the treatment to the administration of a single dose
(Gropper, Raisz, Ampacher).

Polyvinylpyrrolidone solutions have received more attention than any
other high-polymer blood substitutes. Polyvinylpyrrolidone is a product of
the polymerization of vinylpyrrolidone. A 2.5% solution of polyvinylpyrroli-
done in a complex salt mixture was originally applied as a blood substitute
in Germany in 1943. This solution received the name of Periston there. In
subsequent years, polyvinylpyrollidone solutions have been introduced in other
countries.

Experimental tests carried out on polyvinylpyrrolidone demonstrated
that it is highly effective when administered subsequently to shock or blood
losses. However, one must note that dogs on the whole do not stand this prep-
aration very well and that one should use other experimental animals rather than
dogs in work with it (Clark, Malherbe, Weiss). At present, polyvinylpyrrolidone
is supplied by various companies under different names, such as Polydon, Polyvi-
don, Plasmosan, etc., (Arden, Mandon, Staneham, Thrower and Campbell). These
solutions differ from each other in regard to the composition of the salt mix-
tures in which the polyvinylpyrrolidone is dissolved and also as far as the mole-
cular weight of the high polymer is concerned. All these solutions, particularly
periston, have been applied in thousands of clinical cases. It was established
that they are very effective in traumatic shock, subsequently to blood losses,
in burns, in the treatment of intoxications, and in a number of severe surgical
injuries (I. F. Leont'yev).

Just like all other high-polymer colloids which are foreign to the
organism, this preparation has the drawback that it may accumulate in the organs
and tissues of patients and be retained there for a long time (Steele, Van Slyke,
Plarin). However, this drawback may be eliminated by preparing a solution with
a definite, strictly controlled molecular weight within the range of 20,000-
70,000. Solutions of polyvinylpyrrolidone which have been prepared in this manner
have a minimal harmful effect and exhibit only the positive characteristics of
these solutions (Loeffler, Milligan, Stohlman, Morwy, Reinhold, Ravin, Selignan,
Fein).

A solution of this type was subjected to experimental tests on animals
at the Leningrad Institute of Blood Transfusion in 1951. This solution was named
SK, i.e., synthetic colloid (L. G. Bogomolova, I. R. Petrov, Z. A. Chaplygina).
The polymer was prepared at the Institute of High-Molecular Compounds, Academy
of Sciences USSR (S. N. Ushakov, L. V. Davidenkova). The effectiveness of SK
solutions in the treatment of consequences of blood losses was found to be good
and no harmful effects were observed after their infusion. Because of the dif-
ficulty of preparing the SK solution, it was not possible to organize the produc-
tion of this blood substitute in a sufficient quantity for clinical investigation
at that time.

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Cooperation between the Laboratory of Vinyl Compounds, Institute of Organic Chemistry of the Academy of Sciences USSR, and the Laboratory of Physical Chemistry of TsOLIPK has resulted in the determination of conditions under which preparations of polyvinylpyrrolidone having different molecular weights can be obtained (M. S. Shostakovskiy, P. S. Vasil'yev, F. P. Sidel'kovskaya, and Ye. S. Morgunova). The blood substitute solution which has been developed proved to be very effective in controlling the effects of lethal blood losses. It raised effectively and sustained for a long time at the raised level the initially lowered blood pressure of experimental animals (V. B. Koziner, M. G. Zelenskaya). Work with this blood substitute must definitely be continued.

The subgroup of pharmacodynamically active blood substitutes comprises mainly solutions which act on the capillary blood vessels. Their infusion brings about contraction of the capillaries, so that the transfer of liquid out of the blood circulation system is impeded. Preparations of this type are Subsidon and Adrenoxyl (Lang, Heymans, and Charlier). One cannot as yet arrive at a definite conclusion in regard to the value of solutions of this type. However, the possibility of using the underlying idea in the preparation of new blood substitutes should not be overlooked. One must first of all subject to investigation solutions containing rutin.

As far as blood substitute solutions derived from proteins are concerned, much attention has been paid to those derived from heterogenous proteins.

The problem of using heterogenous proteins was originally investigated by I. F. Leont'yev. The solution of Naprin (nonantigenic protein), which he proposed as early as 1935, is the first preparation of this type. Subsequently, useful suggestions have been made by Langenhager in regard to the elimination of the anaphylactogenic properties of heterogenous proteins by the thermal treatment of a solution of dry serum.

In 1941, work on the subject was begun at the Leningrad Institue of Blood Transfusion (L. G. Bogomolova, A. N. Filatov). Work in this field was expanded and proceeded on an extensive scale after cattle serum treated with formaldehyde had been first used for the preparation of such solutions (Edwards).

During World War II Colloidal Infusin was developed at the Central Institute of Blood Transfusion (A. A. Fedorov, P. S. Vasil'yev). Colloidal Infusin is a colloidal-salt solution prepared from casein which has been freed of its antigenic properties. Experimental and clinical investigation of this solution demonstrated its high effectiveness as a blood substitute. It proved effective in the treatment of the hypoproteinemia which develops subsequently to burns and in septic conditions (Kh. Kh. Vlados). Work carried out by V. M. Rodionov confirmed the effectiveness of Colloidal Infusin. At the same time, this work showed that Colloidal Infusin is not fully devoid of toxicity and anaphylactogenic characteristics. Work on this solution must be considerably expanded.

Of great importance in developments pertaining to blood substitutes was work by N. G. Belen'kiy, who proposed in 1945 the species-nonspecific serum.

Subsequently it was found necessary to change the name of the preparation, because the species characteristics of the heterogenous proteins used in this serum could not be completely eliminated. In accordance with the decision of the Scientific Council, this preparation is now referred to as the therapeutic serum prepared according to N. G. Belen'kiy's procedure (LSB). There have been considerable differences of opinion during recent years in regard to the advantages and shortcomings of LSB. All those who have applied LSB are in agreement that the therapeutic effectiveness of the preparation is good and that it can be successfully used in the therapy of shock, consequences of blood losses, debilitation, intoxications, dehydration, burns, and a number of other conditions and diseases (D. A. Arapov, K. S. Simonyan, F. G. Uglov, N. I. Blinov, N. N. Milostanov,

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M. I. Chernenko, and others). However, many authors indicate that notwithstanding the advantages of this serum, one must recognize that reactions ranging up to the acute anaphylactic may arise upon infusion of LSB (Z. F. Saksen, V. A. Severov and F. A. Yuzefovich, I. V. Zaretskiy, I. V. Tatkalo and V. T. Ramazyan, P. K. D'yachenko, A. N. Filatov, N. L. Garfunkel', and L. A. Danilova).

In view of the fact that LSB is not devoid of anaphylactogenic properties, the fact that reactions arise after its use is completely understandable.

During recent years, N. G. Belen'kiy changed to some extent the technological procedures for the production for LSB and succeeded in reducing the deficiencies of this preparation. However, he has not as yet succeeded in making the preparation completely safe (L. N. Pushkar' and A. I. Tarakanov). The task which must be accomplished consists in further work on the improvement of the technology of the production of LSB with the view of completely eliminating all shortcomings of this preparation.

Other solutions of this type, i.e., solutions in which the active component is denatured heterogenous protein, include the Neophylactogenic Serum S-24 and the protein solutions developed by TsOLKP, the BK-8 serum of the Kiev Institute of Blood Transfusion, the German Adequan, the British heterogenous plasma (PH), the Spanish animal plasma which has been rendered nonspecific, the Czechoslovak denatured plasma, the KS-120 solution of the Leningrad Institute of Blood Transfusion, Parenterin, etc., (P. R. Vasil'yev et al., N. A. Fedorov, N. G. Belen'kiy, L. G. Bogomolova, V. A. Belitser, K. I. Katkova, T. K. Gnedash, A. E. Chernyavskiy and A. F. Cheremukhin, D. M. Grozdov, A. A. Fedorovskiy et al., Lewis, Melke, Papont, Zapletan, Weitz, Siebert, and Englehardt).

In the preparation of many of these blood substitutes, treatment in which the proteins are subjected to the action of formalin and of high temperatures is resorted to. However, this treatment does not wholly eliminate the antigenic properties of the heterogenous proteins, so that the method in question cannot be regarded as promising (Bing, Bosser, Larsen, Niessen, Hoet, and others).

A final conclusion in regard to the value of preparations of this type will be possible only at a later stage, after the preparations have been subjected to further and more extensive clinical tests. At present, one cannot but agree with the opinion of one of the German authors (Gruening) who stated in regard to Adequan, which is highly praised in Germany: "Adequan does not represent the ultimate development: further search for new protein blood substitutes solutions is necessary."

Lately considerable attention has been paid to the application of protein hydrolyzates as blood substitutes. Many solutions of protein hydrolyzates are already available. Some of them have been developed abroad (Amigen, etc.), while others have been developed in the USSR. Two solutions of this type which are supplied ready for use have been developed at the Leningrad Institute of Blood Transfusion. One of them is the L-103 solution, which represents an incompletely hydrolyzed product of animal blood treated with acid. Another solution of the Leningrad Institute of Blood Transfusion is also a protein hydrolyzate. This solution has been named Aminol, and is obtained by subjecting animal blood to enzymatic hydrolysis (I. G. Andrianova). The enzymatic hydrolysis is effected by means of swine pancreas. Aminopeptide is also an enzymatic hydrolyzate. The hydrolyzate developed at TsOLIPK is a product of the acid hydrolysis of casein. Because of the efficient technological procedure used for the preparation of this hydrolyzate all essential amino acids are fully retained in it, just as they are in the acid hydrolyzate solution L-103. N. A. Fedorov and V. V. L'vova have subjected to investigation parenteral nutrition with the protein hydrolyzates developed by TsOLIPK and LIPK (L-103). They found under experimental conditions that both solutions have very good nutritional properties and are well assimilated by an organism in the state of starvation.

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Extensive clinical observations in connection with the application of the L-103 solution have clearly shown that this solution has very good therapeutic properties in preventing the development of shock. When administered by the drip method during major operations, it compensates effectively disturbances resulting from blood losses and from shock of a medium degree. It also has excellent nutritive characteristics and is useful in the preparation for surgical operations and during the postoperational period (I. R. Petrov, L. G. Bogomolova, Z. A. Chaplygina, A. M. Romanova, and P. K. D'yachenko). The enzymatic hydrolyzates Amynol and Aminopeptide have also been investigated rather fully under experimental conditions. They do not exert any toxic or anaphylactogenic effects and are well assimilated by the organism. Clinical investigation of these solutions is in process.

The problem of the clinical application of hydrolyzates is only entering the initial phase in the USSR. Extensive developments may be expected in this field. It has not yet been decided whether hydrolyzates should be regarded as true plasma expanders or only as nutrient solutions. The data of US investigators who applied Amigen (an enzymatic hydrolyzate of casein) and work done by investigators of the Leningrad Institute of Blood Transfusion indicate that hydrolyzate solutions can be successfully used for the therapy of consequences of blood losses of a medium degree, the prophylaxis of shock and the therapy of intoxications and sepsis as well as of other pathological conditions.

It is known that protein hydrolyzates exert a pronounced stimulating effect (L. Z. Geykhman). For that reason they can be used as stimulants of the functions of many organs and systems.

N. A. Fedorov and other pathophysiologists do not recognize that hydrolyzates have a range of activity as extensive as this and regard them as nutrient solutions only. The future will show which opinion is better justified.

Blood substitute solutions derived from gelatin are regarded as the most effective by many investigators. Solutions of this type are extensively used in the US in the treatment of shock and of the consequences of blood losses, burns, and intoxications (Milton, Varder, Stanley, Boyd, Popper, Volk, Meyer, and others). Because of special treatment and purification, the gelatin solutions which are available at present are devoid of toxic and anaphylactogenic properties: they do not cause any injury to the organism, something that occurred rather frequently before. The best results were reportedly achieved with the use of solutions of the so called oxypolygelatin and with solutions of modified liquid gelatin (Chen, Lin, Chang, Berlin, Parkins, Perlutt, Vars, Raisz, and others).

3. Blood Substitute Solutions Consisting of Several Ingredients

The Leningrad Institute of Blood Transfusion has proposed up to date several solutions consisting of a number of ingredients. The most promising of them is the Aminoprotein solution, which consists of an L-103 solution to which 1% by volume of human plasma has been added. By reason of the addition of plasma, this solution possesses colloidal properties and is resorbed by the organism more effectively. The second solution consisting of several ingredients is UBP, which is a carbohydrate-protein-plasma blood substitute. It consists of Sinkol and human blood plasma. This solution exhibits superior therapeutic effectiveness and must be regarded as being of considerable value. Bowman combined a dextran solution with modified globin prepared from human blood. Infusion of this solution yielded excellent results.

Sichholtz regards the infusion of periston combined with a small quantity of human blood as of great advantage. This solution rapidly eliminates disturbances of respiration in acute shock.

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Mixed solutions can be prepared immediately before their administration. For that reason it is of importance from the practical standpoint to have a supply of standard solutions which can be combined prior to use.

In conclusion one may state that extensive scientific research work on blood expanders has been carried out in the USSR during recent years. Soviet scientists have already developed a great number of new blood substitute solutions at the present stage. In the near future, production on a large scale of the most effective of them will begin.

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